GB04/04816

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

REC'D 28 DEC 2004
WIPO PCT

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed Stephen Hordley

Dated 24 November 2004

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

tents Form 1/77

nts Act 1977
e 16)

1/77

17NOV03 E857473-1 002639
P01/7700 0.00-0326634.3

:quest for grant of a patent

the notes on the back of this form. You can also get
xplanatory leaflet from the Patent Office to help
fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

Your reference	T1639PV
Patent application number (The Patent Office will fill in this part)	14 NOV 2003 0326634.3
Full name, address and postcode of the or of each applicant (underline all surnames)	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom
'atents ADP number (if you know it)	00597799001
f the applicant is a corporate body, give the ountry/state of its incorporation	United Kingdom
Title of the invention	Therapeutic agents
Name of your agent (if you have one)	Mr. J. Horgan
Address for service" in the United Kingdom) which all correspondence should be sent ncluding the postcode)	Merck & Co., Inc. European Patent Department Terlings Park Eastwick Road Harlow Essex CM20 2QR
'atents ADP number (if you know it)	07536832001

f you are declaring priority from one or more earlier patent applications, give the country nd the date of filing of the or of each of these earlier applications and (if you know it) the or ach application number	Country	Priority Application number (if you know it)	Date of filing (day/month/year)

If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of he earlier application	Number of earlier application	Date of filing (day/month/year)

's a statement of inventorship and of right o grant of a patent required in support of his request? (Answer 'Yes' if:	Yes

any applicant named in part 3 is not an inventor, or
there is an inventor who is not named as an applicant, or
any named applicant is a corporate body.
:e note (d))

tents Form 1/77

Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	35
Claim(s)	0
Abstract	0
Drawing(s)	0

SIO

If you are also filing any of the following, state how many against each item.

Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	-
Request for preliminary examination and search (Patents Form 9/77)	-
Request for substantive examination (Patents Form 10/77)	-
Any other documents (please specify)	-

I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 14 November 2003

Mr. J. Horgan

Name and daytime telephone number of person to contact in the United Kingdom — Mr. J. Horgan — 01279 440625

'arning

'ter an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication · communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You ill be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the nited Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting ritten permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the nited Kingdom for a patent for the same invention and either no direction prohibiting publication or mmunication has been given, or any such direction has been revoked.

otes

- *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*
- *Write your answers in capital letters using black ink or you may type them.*
- *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*
- *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*
- *Once you have filled in the form you must remember to sign and date it.*

For details of the fee and ways to pay please contact the Patent Office.

THERAPEUTIC AGENTS

The present invention is concerned with 2,3-substituted fused bicyclic pyrimidin-4(3H)-ones and analogues and derivatives thereof as well as pharmaceutically acceptable salts and prodrugs thereof, which are useful as therapeutic compounds, particularly in the treatment of pain and other conditions ameliorated by the modulation of the function of the vanilloid-1 receptor (VR1).

The pharmacologically active ingredient of chilli peppers has been recognised for some time to be the phenolic amide capsaicin. The application of capsaicin to mucous membranes or when injected intradermally, causes intense burning-like pain in humans. The beneficial effects of topical administration of capsaicin as an analgesic is also well established. However, understanding of the underlying molecular pharmacology mediating these responses to capsaicin has been a more recent development.

The receptor for capsaicin, termed the vanilloid VR1 receptor, was cloned by Caterina and colleagues at UCSF in 1997 (*Nature,* 398:816, 1997). VR1 receptors are cation channels that are found on sensory nerves that innervate the skin, viscera, peripheral tissues and spinal cord. Activation of VR1 elicits action potentials in sensory fibres that ultimately generate the sensation of pain. Importantly the VR1 receptor is activated not only by capsaicin but also by acidic pH and by noxious heat stimuli. It is also sensitized by a number of inflammatory mediators and thus appears to be a polymodal integrator of painful stimuli.

The prototypical VR1 antagonist is capsazepine (Walpole *et al.*, *J. Med. Chem.,* 37:1942, 1994) – VR1 IC_{50} of 420nM. A novel series of sub-micromolar antagonists has also been reported recently (Lee *et al*, *Bioorg. Med. Chem.*, 9:1713, 2001), but these reports provide no evidence for *in vivo* efficacy. A much higher affinity antagonist has been derived from the 'ultra-potent' agonist resiniferatoxin. Iodo-resiniferatoxin (Wahl *et al.*, *Mol. Pharmacol.*, 59:9, 2001) is a nanomolar antagonist of VR1 but does not possess properties suitable for an oral pharmaceutical. This last is also true of the micromolar peptoid antagonists described by Garcia-Martinez (*Proc. Natl. Acad. Sci., USA,* 99:2374, 2002).

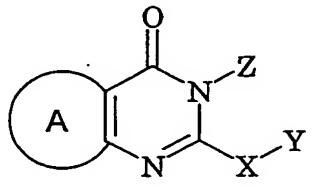
EP-A-0807633 (Pfizer Inc.) discloses structurally related AMPA receptor antagonists for treating neurodegenerative and CNS-trauma related conditions.

WO-A-9733890 (Novartis AG) discloses structurally related compounds as pesticides.

The compounds of the present invention have advantageous properties, such as good metabolic stability.

We herein describe another novel series of VR1 modulators. These comprise predominantly VR1 antagonists but encompass VR1 partial antagonists and VR1 partial agonists. Such compounds have been shown to be efficacious in animal models of pain.

The present invention provides compounds of formula I:



(I)

wherein:

A is a benzene ring, a fused five-membered heteroaromatic ring containing 1, 2 or 3 heteroatoms independently chosen from O, N and S, providing that no more than one O or S atom is present, or a fused six-membered heteroaromatic ring containing 1, 2 or 3 N atoms;

A is optionally substituted by one, two or three groups independently chosen from halogen, hydroxy, phenyl, $S(O)_rC_{1-4}$alkyl, $S(O)_rNR^5R^6$, formyl, C_{1-4}alkylcarbonyl, C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{3-7}cycloalkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, amino, nitro, cyano, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl and aminoC_{1-6}alkoxy;

X is O, S or NR^1 where R^1 is hydrogen or C_{1-6}alkyl;

Y is $(CR^2R^3)_n(CO)_p(NR^4)_qW$;

R^2 and R^3 are independently hydrogen, halogen or C_{1-4}alkyl;

R^4 is hydrogen or C_{1-6}alkyl;

n is one, two, three or four;

p is zero or one;

q is zero or one;

r is zero, one or two;

W is hydrogen, C_{1-6}alkoxy, C_{1-6}alkyl; or a phenyl ring, a five-membered heteroaromatic ring containing one, two, three or four heteroatoms independently chosen from O, N and S, at most one heteroatom being O or S, a six-membered heteroaromatic ring containing one, two or three N atoms, or a nine- or ten-membered fused bicyclic heteroaromatic ring containing a phenyl ring or a six-membered heteroaromatic ring as just defined, fused to either a six-membered heteroaromatic ring as just defined or a five-membered heteroaromatic ring as just defined, the ring being optionally substituted by halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, nitro, cyano, C_{3-7}cycloalkyl, hydroxy, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, phenyl, an unsubstituted five-membered heteroaromatic ring as just described, a six-membered heteroaromatic ring as just described or NR^5R^6;

each R^5 and R^6 is independently hydrogen or C_{1-6}alkyl or R^5 and R^6, together with the nitrogen atom to which they are attached, may form a saturated 4-7 membered ring;

Z is a phenyl ring, a five-membered heteroaromatic ring containing one, two, three or four heteroatoms independently chosen from O, N or S, at most one heteroatom being O or S, a six-membered heteroaromatic ring containing one, two or three N atoms, optionally substituted by halogen, hydroxy, cyano, nitro, NR^5R^6 as defined above, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{3-7}cycloalkyl or hydroxyC_{1-6}alkyl;

when R^1 and R^4 are alkyl groups they may, together with the nitrogen atoms to which they are attached, form a piperazine ring;

or a pharmaceutically acceptable salt thereof.

A may be a benzene ring, a fused five-membered heteroaromatic ring containing 1, 2 or 3 heteroatoms independently chosen from O, N and S, providing that no more than one O or S atom is present, or a fused six-membered heteroaromatic ring containing 1, 2 or 3 N atoms.

A is preferably unsubstituted or substituted by halogen, hydroxy, C_{3-5}cycloalkyl, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxy or haloC_{1-4}alkoxy. More preferably A is unsubstituted or substituted by halogen or C_{1-4}alkyl. A is preferably unsubstituted or substituted by methyl. In one embodiment A is not thiophene.

A is preferably a fused pyridine, thiophene, thiazole or imidazole.

X may be O. X may be S. X may be NH.

R^1 is preferably hydrogen or C_{1-2}alkyl. R^1 may be hydrogen.

R^2 and R^3 are preferably hydrogen, halogen or methyl. R^2 and R^3 are most preferably hydrogen.

R^4 is preferably hydrogen or C_{1-2}alkyl. R^4 may be hydrogen.

R^1 and R^4, together with the nitrogen atoms to which they are attached, may form a piperazine ring, such as a piperazinone ring.

n is preferably one or two.

Particular embodiments of $(CR^2R^3)_n(CO)_p(NR^4)_q$ include CH_2, CH_2CO, CH_2CH_2 and CH_2CONH.

In one embodiment W is not hydrogen or C_{1-6}alkyl.

W is preferably unsubstituted or substituted by halogen, C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, haloC_{1-4}alkyl, phenyl, haloC_{1-4}alkoxy or NR^5R^6 where R^5 and R^6 are independently C_{1-4}alkyl or, R^5 and R^6, together with the nitrogen atom to which they are attached, form a 5-6 membered saturated ring. More preferably W is unsubstituted or substituted by halogen, C_{1-2}alkyl, C_{1-2}haloalkyl, C_{1-2}alkoxy or phenyl. If substituted W is preferably monosubstituted. W may be disubstituted. Particular substituents include fluorine, chlorine, trifluoromethoxy, trifluoromethyl, pyrrolidine, methyl and phenyl.

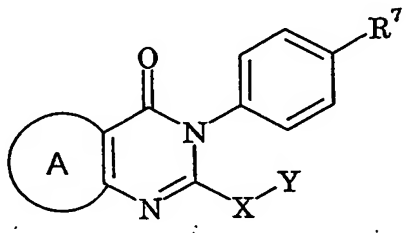
Particular aromatic W rings include benzene, benzothiazole, benzothiophene, pyridine, 1,2,4-oxadiazole and isoxazole.

Particular embodiments of W include methyl, 3-fluorophenyl, 4-chlorophenyl, 5-chloro-1-benzothien-3-yl, 1-benzothien-3-yl, 1,3-benzothiazol-2-yl, phenyl, 3-chlorophenyl, 4-trifluoromethoxyphenyl, 4-trifluoromethylphenyl, 4-pyrrolidin-1-ylphenyl, pyrid-2-yl, 4-fluorophenyl, 5-phenyl-1,2,4-oxadiazol-3-yl and 5-methylisoxazol-3-yl.

Z is preferably unsubstituted or substituted by one substituent chosen from cyano, halogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxy and haloC_{1-4}alkoxy. Z is

preferably monosubstituted. Z is preferably a phenyl ring. Preferred substituents are chlorine and trifluoromethyl. Particular embodiments of Z are 4-chlorophenyl and 4-trifluoromethylphenyl.

The present invention also provides compounds of formula IA:



(IA)

wherein A is a fused five-membered heteroaromatic ring containing 1, 2 or 3 heteroatoms independently chosen from O, N and S, providing that no more than one O or S atom is present, or a fused six-membered heteroaromatic ring containing 1, 2 or 3 N atoms;

A is optionally substituted by halogen or C_{1-4}alkyl;

X is O, S or NR^1 where R^1 is hydrogen or C_{1-4}alkyl;

Y is $(CR^2R^3)_n(CO)_p(NR^4)_qW$, where R^2, R^3, R^4, n, p and q are as defined for formula I;

W is C_{1-6} alkyl; or a phenyl ring, a five-membered heteroaromatic ring containing one, two, three or four heteroatoms independently chosen from O, N or S, at most one heteroatom being O or S, a six-membered heteroaromatic ring containing one, two or three N atoms, or a nine- or ten-membered fused bicyclic heteroaromatic ring containing a phenyl ring or a six-membered heteroaromatic ring as just defined, fused to either a six-membered heteroaromatic ring as just defined or a five-membered heteroaromatic ring as just defined, the ring being optionally substituted by halogen, C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, haloC_{1-4}alkyl, phenyl, haloC_{1-4}alkoxy or NR^5R^6 where R^5 and R^6 are independently C_{1-4}alkyl or, R^5 and R^6, together with the nitrogen atom to which they are attached, form a 5-6 membered saturated ring;

R^7 is hydrogen, cyano, halogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxy or haloC_{1-4}alkoxy;

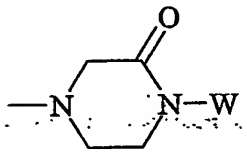
when R^1 and R^4 are alkyl groups they may, together with the nitrogen atoms to which they are attached, form a piperazine ring;

or a pharmaceutically acceptable salt thereof.

A is preferably a fused pyridine, thiophene, thiazole or imidazole which is unsubstituted or substituted by halogen or methyl.

R^1 is preferably hydrogen or C_{1-2}alkyl, most preferably hydrogen.

Y is preferably CH_2W, CH_2COW, CH_2CH_2W or CH_2CONHW, or X-Y is



W is preferably unsubstituted or substituted by halogen, C_{1-2}alkyl, C_{1-2}haloalkyl, C_{1-2}alkoxy or phenyl. More preferably W is unsubstituted or monosubstituted by fluorine, chlorine, trifluoromethoxy, trifluoromethyl, pyrrolidine, methyl or phenyl.

W is preferably a benzene, benzothiazole, benzothiophene, pyridine, 1,2,4-oxadiazole or isoxazole ring.

R^7 is preferably chlorine or trifluoromethyl.

Particular embodiments of the invention include:

3-(4-chlorophenyl)-2-[3-fluorobenzylthio]pyrido[3,4-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-{2-(4-chlorophenyl)-2-oxoethylthio}pyrido[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-[3-fluorobenzylthio]pyrido[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-{2-(4-chlorophenyl)ethylthio}pyrido[3,2-d]pyrimidin-4(3H)-one;

2-{5-chloro-1-benzothien-3-ylmethylthio}-3-(4-chlorophenyl)pyrido[3,2-d]pyrimidin-4(3H)-one;

2-[1-benzothien-3-ylmethyl)thio]-3-(4-chlorophenyl)pyrido[3,2-d]pyrimidin-4(3H)-one;

2-[1,3-benzothiazol-2-ylmethylthio]-3-(4-chlorophenyl)pyrido[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-[2-oxo-2-phenylethylthio]pyrido[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-{2-(3-chlorophenyl)-2-oxoethylthio}pyrido[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-(2-oxo-2-[4-trifluoromethoxyphenyl]ethylthio)pyrido[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-(2-oxo-2-[4-trifluoromethylphenyl]ethylthio)pyrido[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-{2-oxo-2-(4-pyrrolidin-1-ylphenyl)ethylthio}pyrido[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-[2-oxo-2-pyridin-2-ylethylthio]pyrido[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-[4-fluorobenzylthio]pyrido[3,2-d]pyrimidin-4(3H)-one;

2-[3-chlorobenzylthio]-3-(4-chlorophenyl)pyrido[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-[pyridin-2-ylmethylthio]pyrido[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-{5-phenyl-1,2,4-oxadiazol-3-ylmethylthio}pyrido[3,2-d]pyrimidin-4(3H)-one;

2-{3-(4-chlorophenyl)-4-oxo-3,4-dihydropyrido[3,2-d]pyrimidin-2-ylthio}-N-(5-methylisoxazol-3-yl)acetamide;

3-(4-chlorophenyl)-2-[3-fluorobenzylthio]thieno[2,3-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-[3-fluorobenzylthio]thieno[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-{2-(4-chlorophenyl)-2-oxoethylthio}thieno [3,2-d]pyrimidin-4(3H)-one;

6-(4-chlorophenyl)-5-[3-fluorobenzylthio][1,3]thiazolo[5,4-d]pyrimidin-7(6H)-one;

6-(4-chlorophenyl)-5-{2-(4-chlorophenyl)-2-oxoethylthio}[1,3]thiazolo[5,4-d]pyrimidin-7(6H)-one;

6-(4-chlorophenyl)-5-{2-(4-chlorophenyl)-2-oxoethylthio}[1,3]thiazolo[4,5-d]pyrimidin-7(6H)-one;

2-{5-chloro-1-benzothien-3-ylmethylthio}-1-(4-chlorophenyl)-9-methyl-1,9-dihydro-6H-purin-6-one;

1-(4-chlorophenyl)-9-methyl-2-(2-[4-trifluoromethylphenyl]ethylthio)-1,9-dihydro-6H-purin-6-one;

1-(4-chlorophenyl)-2-{2-(4-chlorophenyl)ethylthio}-9-methyl-1,9-dihydro-6H-purin-6-one;

1-(4-chlorophenyl)-2-{2-(4-chlorophenyl)-2-oxoethylthio}-9-methyl-1,9-dihydro-6H-purin-6-one;

1-(4-chlorophenyl)-2-[3-fluorobenzylthio]-9-methyl-1,9-dihydro-6H-purin-6-one;

1-(4-chlorophenyl)-2-[3-fluorobenzylthio]-1,9-dihydro-6H-purin-6-one;

2-{2-(4-chlorophenyl)-2-oxoethylthio}-3-[4-trifluoromethylphenyl]pyrido[3,2-d]pyrimidin-4(3H)-one;

2-[3-fluorobenzylthio]-3-[4-trifluoromethylphenyl]pyrido[3,2-d]pyrimidin-4(3H)-one;

2-(methylthio)-3-pyridin-3-ylpyrido[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-(3-oxo-4-phenylpiperazin-1-yl)pyrido[3,2-d]pyrimidin-4(3H)-one;

3-4-chlorophenyl-2-{2-(4-chlorophenyl)ethylamino}pyrido[3,2-d]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-[3-fluorobenzyloxy]thieno[3,2-*d*]pyrimidin-4(3*H*)-one; and

3-(4-chlorophenyl)-2-[3-fluorobenzylamino]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

or a pharmaceutically acceptable salt thereof.

As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

As used herein, the terms "haloC_{1-6}alkyl" and "haloC_{1-6}alkoxy" means a C_{1-6}alkyl or C_{1-6}alkoxy group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by halogen atoms, especially fluorine or chlorine atoms. Preferred are fluoroC_{1-6}alkyl and fluoroC_{1-6}alkoxy groups, in particular, fluoroC_{1-3}alkyl and fluoroC_{1-3}alkoxy groups, for example, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, OCF_3, OCH_2CH_2F, OCH_2CHF_2 or OCH_2CF_3, and most especially CF_3 and OCF_3.

The cycloalkyl groups referred to herein may represent, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Such groups also include, for example, cyclopropylmethyl and cyclohexylmethyl.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part of a group means that the group is straight or branched. Examples of suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is acetylene or propargyl.

When used herein, the term "halogen" means fluorine, chlorine, bromine and iodine. The most preferred halogens are fluorine and chlorine, especially chlorine.

Examples of 6-membered heterocycles are pyridine, pyrimidine, pyrazine, pyridazine and triazine.

Examples of 5-membered heterocycles are thiophene, furan, pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, 1,2,3-triazole, 1,2,4-triazole, oxadiazole, thiadiazole and tetrazole.

Examples of 9- or 10-membered fused bicyclic heteroaromatic rings include benzofuran, benzothiophene, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, quinoline, isoquinoline and cinnoline.

In a further aspect of the present invention, the compounds of formula I may be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The salts may be formed by conventional means, such as by reacting the free base form of the compound of formula I with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

The present invention also includes within its scope N-oxides of the compounds of formula I above. In general, such N-oxides may be formed on any available nitrogen atom. The N-oxides may be formed by conventional means, such as reacting the compound of formula I with oxone in the presence of wet alumina.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

The present invention includes within its scope solvates of the compounds of formula I and salts thereof, for example, hydrates.

The compounds according to the invention may have one or more asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, the compounds of formula I may also exist in tautomeric forms and the invention includes within its scope both mixtures and separate individual tautomers.

The compounds may exist in different isomeric forms, all of which are encompassed by the present invention.

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula I in association with a pharmaceutically acceptable carrier or excipient.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-

injector devices, suppositories, creams or gels; for oral, parenteral, intrathecal, intranasal, sublingual, rectal or topical administration, or for administration by inhalation or insufflation. Oral compositions such as tablets, pills, capsules or wafers are particularly preferred. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tabletting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid pre-formulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these pre-formulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid pre-formulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Favoured unit dosage forms contain from 1 to 500 mg, for example 1, 5, 10, 25, 50, 100, 300 or 500 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums

such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of painful conditions such as those listed below, a suitable dosage level is about 1.0 mg to 15 g per day, preferably about 5.0 mg to 1 g per day, more preferably about 5 mg to 500 mg per day, especially 10 mg to 100 mg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

It will be appreciated that the amount of a compound of formula I required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

The invention further provides a compound of formula I as defined above, or a pharmaceutically acceptable salt thereof, for use in treatment of the human or animal body. Preferably, said treatment is for a condition which is susceptible to treatment by modulation (preferably antagonism) of VR1 receptors.

The compounds of the present invention will be of use in the prevention or treatment of diseases and conditions in which pain and/or inflammation predominates, including chronic and acute pain conditions. Such conditions include rheumatoid arthritis; osteoarthritis; post-surgical pain; musculo-skeletal pain, particularly after trauma; spinal pain; myofascial pain syndromes; headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain; ear pain; episiotomy pain; burns, and especially primary hyperalgesia associated therewith; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for example, dysmenorrhoea, pain associated with cystitis and labour pain, chronic pelvic pain, chronic prostatitis and endometriosis; pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; itching conditions including pruritis, itch due to hemodialysis, and contact dermatitis; pain (as well as broncho-constriction and inflammation) due to exposure (e.g. via ingestion, inhalation, or eye contact) of mucous

membranes to capsaicin and related irritants such as tear gas, hot peppers or pepper spray; neuropathic pain conditions such as diabetic neuropathy, chemotherapy-induced neuropathy and post-herpetic neuralgia; "non-painful" neuropathies; complex regional pain syndromes; pain associated with carcinoma, often referred to as cancer pain; central nervous system pain, such as pain due to spinal cord or brain stem damage, low back pain, sciatica and ankylosing spondylitis; gout; scar pain; irritable bowel syndrome; inflammatory bowel disease; urinary incontinence including bladder detrusor hyper-reflexia and bladder hypersensitivity; respiratory diseases including chronic obstructive pulmonary disease (COPD), chronic bronchitis, cystic fibrosis, asthma and rhinitis, including allergic rhinitis such as seasonal and perennial rhinitis, and non-allergic rhinitis; autoimmune diseases; and immunodeficiency disorders.

Thus, according to a further aspect, the present invention provides a compound of formula I for use in the manufacture of a medicament for the treatment or prevention of physiological disorders that may be ameliorated by modulating VR1 activity.

The present invention also provides a method for the treatment or prevention of physiological disorders that may be ameliorated by modulating VR1 activity, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

According to a further or alternative aspect, the present invention provides a compound of formula I for use in the manufacture of a medicament for the treatment or prevention of a disease or condition in which pain and/or inflammation predominates.

The present invention also provides a method for the treatment or prevention of a disease or condition in which pain and/or inflammation predominates, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

According to a further aspect of the present invention, it may be desirable to treat any of the aforementioned conditions with a combination of a compound according to the present invention and one or more other pharmacologically active agents suitable for the treatment of the specific condition. The compound

of formula I and the other pharmacologically active agent(s) may be administered to a patient simultaneously, sequentially or in combination.

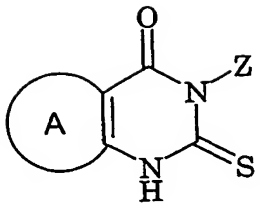
Thus, for example, for the treatment or prevention of pain and/or inflammation, a compound of the present invention may be used in conjunction with other analgesics, such as acetaminophen (paracetamol), aspirin and other NSAIDs, including selective cyclooxygenase-2 (COX-2) inhibitors, as well as opioid analgesics, especially morphine, NR2B antagonists, bradykinin antagonists, anti-migraine agents, anticonvulsants such as oxcarbazepine and carbamazepine, antidepressants (such as TCAs, SSRIs, SNRIs, substance P antagonists, etc.), spinal blocks, gabapentin, pregabalin and asthma treatments (such as β_2-adrenergic receptor agonists or leukotriene D_4 antagonists (e.g. montelukast).

Specific anti-inflammatory agents include diclofenac, ibuprofen, indomethacin, nabumetone, ketoprofen, naproxen, piroxicam and sulindac, etodolac, meloxicam, rofecoxib, celecoxib, etoricoxib, parecoxib, valdecoxib and tilicoxib. Suitable opioid analgesics of use in conjunction with a compound of the present invention include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine; or a pharmaceutically acceptable salt thereof. Suitable anti-migraine agents of use in conjunction with a compound of the present invention include CGRP-antagonists, ergotamines or 5-HT_1 agonists, especially sumatriptan, naratriptan, zolmatriptan or rizatriptan.

Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an analgesic, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an analgesic as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a disease or condition in which pain and/or inflammation predominates.

Compounds of formula I in which X is S can be made by reacting a compound of formula II with a compound of formula III:



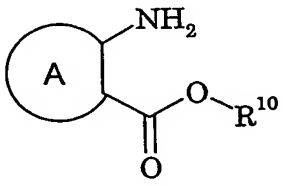
(II)

L^1-Y

(III)

wherein A, Y and Z are as defined above and L^1 is a leaving group such as Cl, Br, or I. The reaction is generally carried out in the presence of a mild base, such as potassium carbonate, in a solvent such as acetonitrile from room temperature to 75°C for two to 24 hours.

Compounds of formula II can be made by reacting a compound of formula IV with a compound of formula V:



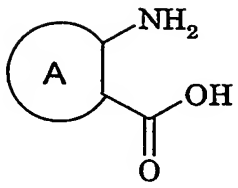
(IV)

Z-NCS

(V)

wherein A and Z are as defined above and R^{10} is a C_{1-6}alkyl group such as methyl. The reaction is generally carried out in a solvent such as acetonitrile, ethanol or pyridine from 45°C to reflux for from 2 to 24 hours. A catalytic amount of a compound such as 4-dimethylaminopyridine is generally added. If necessary the reaction-completing ring closure is effected by the addition of a base such as potassium hydroxide or sodium hydroxide in a solvent such as methanol, water or tetrahydrofuran for from 30 minutes to 3 hours from room temperature to reflux.

The compound of formula IV can be made by reacting a compound of formula VI with an alcohol of formula VII:



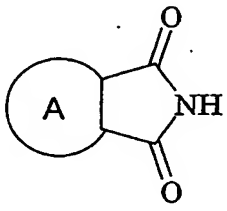
(VI)

$R^{10}OH$

(VII)

wherein A and R^{10} are as defined above, generally in the presence of an acid, such as sulphuric acid, at about 80°C for from 3 to 7 days.

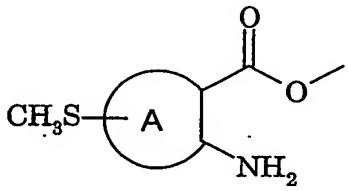
The compound of formula VI can be made by reacting a compound of formula VIII:



(VIII)

wherein A is as defined above, with an oxidizing agent such as sodium hypobromite (which can be prepared by reacting bromine with 10% $NaOH_{(aq)}$ at about 0°C). The reaction is generally carried out at about 80°C for about 45 minutes.

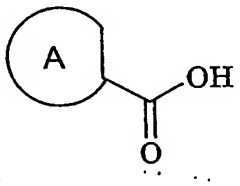
The compound of formula IV can alternatively be prepared by reacting a compound of formula IX:



(IX)

wherein A is as defined above with a hydrogenating agent such as Raney Nickel in the presence of hydrogen at about 45 psi for about 1 week generally in a solvent such as ethanol/water mixture.

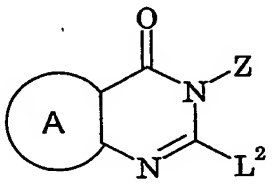
Alternatively the compound of formula IV can be made by reacting a compound of formula X:



(X)

wherein A is as defined above firstly with a nitrating agent such as ammonium nitrate generally in the presence of an acid such as sulphuric acid at about 100°C for about 2 days, secondly with a compound of formula VII under the conditions described for reaction with the compound of formula VI and thirdly under hydrogenating conditions such as hydrogen on 10% Pd/C in a solvent mixture of ethanol and water for about 4 hours.

Compounds of formula I in which X is NR^1, where R^1 is as defined above, can be made by reacting a compound of formula XI with a compound of formula XII:



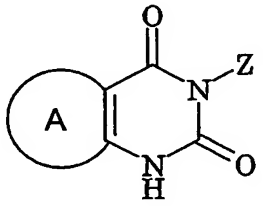
(XI)

$H(R^1)NY$

(XII)

wherein A, R^1, Y and Z are as defined above and L^2 is a leaving group such as chlorine. The reaction is generally carried out in a solvent such as acetonitrile in the presence of a base such as potassium carbonate at about reflux for four or five hours.

Compounds of formula XI can be made by reacting a compound of formula II with a chlorinating agent such as PCl_5 in $POCl_3$ or $POCl_3$ in pyridine at about 100°C or reflux for 6 to 24 hours. They can also be made under the same conditions starting with a compound of formula XIII:



(XIII)

wherein A and Z are as defined above.

Compounds of formula XIII can be made in the same way as compounds of formula II but using a compound of formula XIV:

Z-NCO

(XIV)

wherein Z is as defined above generally in a solvent such as ethyl acetate at about reflux for about 8 hours, followed by a ring closure as described for the preparation of compounds of formula II.

Compounds of formula I in which X is O can be prepared by reacting a compound of formula XI with a compound of formula XV:

HOY

(XV)

wherein Y is as defined above. The reaction is generally carried out in the presence of a strong base such as sodium hydride in a solvent such as tetrahydrofuran from about 0°C to room temperature for about 18 hours.

Where the synthesis of intermediates and starting materials is not described these compounds are commercially available or can be made from commercially available compounds by standard methods.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples serve to illustrate the preparation of compounds of the present invention.

Description 1 3-Aminoisonicotinic acid

Bromine (3.5 ml, 69.0 mmol) was added to a solution of 10 % aqueous sodium hydroxide (120 ml) at 0 °C to give a pale yellow solution. To this solution was added 3,4-pyridinedicarboximide (10 g, 67.5 mmol) and the reaction was heated at 80 °C for 45 min. The reaction was cooled in a water bath and acidified by the addition of acetic acid (12.5 ml) causing precipitation. The solid was collected, rinsed with water (50 ml), then MeOH (50 ml) and dried to give the title compound as a beige solid (6.28 g, 67 %). ^{1}H NMR (360 MHz, DMSO) δ 8.06 (1H, s), 7.60 (1H, d, *J* 5.1), 7.34 (1H, d, *J* 5.1), 3.19 (2H, brs). *M/z* (ES$^+$) 139 (M+H$^+$).

Description 2 Methyl-3-aminoisonicotinate

Description 1 (3.55 g, 25.7 mmol), H_2SO_4 (2.5 ml) and methanol (50 ml) were heated at 80 °C for 3 days. The methanol was evaporated, the residue diluted with water (75 ml) and heated to 80 °C. Solid sodium carbonate was added until effervescence ceased. The mixture was cooled and extracted with dichloromethane (2 x 100 ml). The combined organic layers were dried over $MgSO_4$ and concentrated to give the title compound as a beige solid (2.36 g, 60 %). ^{1}H NMR (500 MHz, DMSO) δ 8.24 (1H, s), 7.74 (1H, d, *J* 5.3), 7.46 (1H, d, *J* 5.2), 6.67 (2H, brs), 3.83 (3H, s). *M/z* (ES$^+$) 153 (M+H$^+$).

Description 3 3-(4-Chlorophenyl)-2-thioxo-2,3-dihydropyrido[3,4-d]pyrimidin-4(1H)-one

Description 2 (1.86 g, 12.2 mmol) and 4-chlorophenyl isothiocyanate (2.28 g, 13.5 mmol) were heated at 70 °C in acetonitrile (30 ml) with a catalytic amount of 4-dimethylaminopyridine for 24 h. The reaction was cooled and the solid product collected by filtration, washed with ether (20 ml) then dichloromethane (10 ml) and dried to give the title compound as a white solid (2.15 g, 61 %). ^{1}H NMR (500 MHz, DMSO) δ 13.26 (1H, s), 8.79 (1H, s), 8.50 (1H, d, *J* 5.1), 7.79 (1H, d, *J* 5.2), 7.53 (2H, d, *J* 8.6), 7.31 (2H, d, *J* 8.6). *M/z* (ES$^+$) 290 (M+H$^+$).

Description 4 Methyl 3-aminopyridine-2-carboxylate

A solution of 3-aminopyridine-2-carboxylic acid (*Bioorg. Med. Chem.* 2001, 9, 2061) (1.0 g, 7.25 mmol) and H_2SO_4 (2.75 ml) in methanol (15 ml) was heated at 80 °C for 7 days. The reaction was cooled and the methanol removed by evaporation. The residue was poured into water (ca. 30 ml) and solid sodium carbonate was added until effervescence ceased (pH ~7). The mixture was extracted with dichloromethane (4 x 50 ml) and the combined organic fractions dried over $MgSO_4$ and concentrated to give the title compound as a beige solid (0.84 g, 76 %). ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.07 (1H, dd, *J* 4.2, 1.4), 7.22 (1H, dd, *J* 8.4, 4.2), 7.05 (1H, dd, *J* 8.4, 1.4), 5.73 (2H, brs), 3.98 (3H, s). *M/z* (ES$^+$) 153 (M+H$^+$).

Description 5 3-(4-Chlorophenyl)-2-thioxo-2,3-dihydropyrido[3,2-*d*]pyrimidin-4(1*H*)-one

A solution of 4-chlorophenyl isothiocyanate (1.10 g, 6.48 mmol) and ethyl 3-aminopyridine-2-carboxylate (*J. Chem. Soc.* 1956, 1045) (1.07 g, 6.48 mmol) in acetonitrile (30 ml) was heated at reflux for 2 h, then cooled to room temperature. The solid was collected by filtration, washed with cold acetonitrile (5 ml) and dried to give the title compound as a white crystalline solid (84 mg, 4.5 %). The filtrate was re-heated to reflux for 18 h and then cooled to room temperature to give a second crop of crystals. The crystals were collected by filtration, washed with acetonitrile (5 ml) and dried to give the title compound (350 mg, 19 %). ^{1}H NMR (400 MHz, DMSO) δ 13.09 (1H, br. s), 8.60 (1H, dd, *J* 4.3, 1.5), 7.82 (1H, dd,

J 8.4, 1.5), 7.77 (1H, dd, *J* 8.4, 4.3), 7.55 (2H, d, *J* 8.0), 7.35 (2H, d, *J* 8.0). *M/z* (ES+) 290, 292 ($M+H^+$).

Description 6 2-Chloro-3-(4-chlorophenyl)pyrido[3,2-*d*]pyrimidin-4(3*H*)-one

A solution of Description 5 (123 mg, 0.43 mmol) and phosphorous pentachloride (134 mg, 0.65 mmol) in phosphorous oxychloride (1 ml) was stirred at 100 °C for 24 h. The reaction mixture was cooled, evaporated *in vacuo*, and azeotroped twice with toluene. The resulting oil was then dissolved in ethyl acetate (15 ml) and washed with water (5 x 15 ml). The organic layer was dried over $MgSO_4$, filtered and evaporated to give a brown solid. The solid was dry loaded in acetonitrile onto silica and purified by flash column chromatography [eluant: ethyl acetate/ dichloromethane (1:4)] to give the title compound as pale yellow solid (58 mg, 47 %). ^1H NMR (360 MHz, DMSO) δ 8.86 (1H, dd, *J* 4.4, 1.6), 8.16 (1H, dd, *J* 8.2, 1.6), 7.91 (1H, dd, *J* 8.2, 4.4), 7.66 (2H, d, *J* 8.7), 7.58 (2H, d, *J* 8.7): *M/z* (ES+) 292, 294 ($M+H^+$).

Description 7 3-(4-Chlorophenyl)-2-thioxo-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-one

A solution of methyl 2-aminothiophene-3-carboxylate (1.0 g, 6.4 mmol) and 4-chlorophenyl isothiocyanate (1.2 g, 7.1 mmol) in ethanol (10 ml) was stirred at 100 °C for 16 h. The reaction was cooled and the solid collected by filtration, washed with ether and dried to give methyl 2-(4-chlorophenylaminocarbonothioyl amino)thiophene-3-carboxylate as a white solid (0.83 g, 40 %). This solid (0.63 g, 1.93 mmol) was treated with a solution of potassium hydroxide in methanol (2 M, 8 ml) at room temperature for 40 min. The reaction was acidified with 5 M aqueous hydrochloric acid leading to a thick white precipitate. The slurry was diluted with water (25 ml) to dissolve salts and then filtered. The product was washed with water and dried to give the title compound as a white solid (0.45 g, 79 %). ^1H NMR (360 MHz, DMSO) δ 13.82 (1H, s), 7.53 (2H, m), 7.31 (3H, m), 7.24 (1H, d, *J* 5.6). *M/z* (ES+) 295, 297 ($M+H^+$).

Description 8 3-(4-Chlorophenyl)-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(1*H*)-one

A solution of methyl-3-aminothiophene-2-carboxylate (6.79 g, 4.32 mmol) and 4-chlorophenyl isothiocyanate (8.42 g, 49.6 mmol) was treated using the method of Description 7 to give methyl 3-(4-chlorophenylaminocarbonothioyl amino)thiophene-2-carboxylate (6.16 g, 44 %). This solid (4.0 g, 13.6 mmol) was treated with potassium hydroxide as in Description 7 to give the title compound as a white solid (3.42 g, 96 %). ^{1}H NMR (360 MHz, DMSO) δ 13.53 (1H, s), 8.20 (1H, d, *J* 5.2), 7.53 (2H, d, 8.5), 7.32 (2H, d, *J* 8.6), 7.07 (1H d, *J* 5.2). *M/z* (ES$^+$) 295; 297 (M+H$^+$).

Description 9 3-(4-Chlorophenyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

To a solution of methyl 3-aminothiophene-2-carboxylate (5.1 g, 32.5 mmol) and 4-dimethylaminopyridine (50 mg) in EtOAc (50 ml) was added 4-chlorophenyl isocyanate (5 g, 32.5 mmol)) portion-wise. After the addition was complete, the reaction was heated to reflux for 8 h. The reaction was cooled, the white solid collected by filtration and added to a solution of potassium hydroxide (3 g, 53.6 mmol) in THF/water (10:1; 35 ml). The mixture was heated to reflux for 30 min, allowed to cool, acidified with 5 M aqueous hydrochloric acid and the resultant solid collected by filtration and dried to give the title compound as a white solid (2.4 g, 26 %). ^{1}H NMR (360 MHz, DMSO) 12.04 (1H, s), 8.12 (1H, d, *J* 5.4), 7.53 (2H, d, *J* 8.6), 7.36 (2H, d, *J* 8.6), 6.99 (1H, d, *J* 5.3).

Description 10 2-Chloro-3-(4-chlorophenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

A suspension of Description 9 (2.4 g, 8.5 mmol) in phosphorus oxychloride (25 ml) and pyridine (2.5 ml) was heated to reflux for 6 h. After cooling, phosphorus oxychloride was removed *in vacuo* and ice-chilled water (50 ml) added. The reaction was extracted with dichloromethane (3 x 50 ml) and the combined organic fractions were washed with brine, dried over Na_2SO_4, and condensed to give a bright blue solid. The product was purified using a prepacked silica column, eluting with 8-25% ethyl acetate in hexane to provide a white solid (150 mg, 4 %). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.87 (1H, d, *J* 5.3), 7.53 (2H, d, *J* 8.6), 7.34 (1H, d, *J* 5.3), 7.24 (2H, d, *J* 8.6).

Description 11 Ethyl 5-(4-chlorophenylaminocarbonothioylamino)-1,3-thiazole-4-carboxylate

A solution of ethyl 5-amino-1,3-thiazole-4-carboxylate (*Tetrahedron* 1985, 41, 5989) (544 mg, 3.16 mmol) and 4-chlorophenyl isothiocyanate (536 mg, 3.16 mmol) in acetonitrile (15 ml) was heated at reflux for 20 h. The mixture was filtered to remove insoluble material and the filtrate re-heated to reflux for a further 72 h. Flash silica (ca. 10 g) was added and the solvent evaporated. The residue was then purified by flash column chromatography [eluant: ethyl acetate/ isohexane (1:3), then (1:1), then (3:1)] to give the title compound (358 mg, 33 %). ^{1}H NMR (400 MHz, DMSO) δ 11.53 (1H, s), 11.51 (1H, s), 8.47 (1H, s), 7.58 (2H, d, *J* 8.7), 7.47 (2H, d, *J* 8.7), 4.35 (2H, q, *J* 7.0), 1.33 (3H, t, *J* 7.0). *M/z* (ES$^+$) 342, 344 (M+H$^+$).

Description 12 6-(4-Chlorophenyl)-5-thioxo-5,6-dihydro[1,3]thiazolo[5,4-*d*] pyrimidin-7(4*H*)-one

Description 11 (358 mg, 1.05 mmol) was suspended in methanol (15 ml) at room temperature. Methanolic 2 M potassium hydroxide solution (2 ml, 2 mmol) was added and the reaction mixture was stirred for 3 h. The reaction was then cooled to 0 °C and acidified by adding 2 N aqueous hydrochloric acid (ca. 5 ml, 10 mmol). After stirring for 10 min, the solid was collected by filtration and washed with water (3 x 5 ml), then dried under vacuum to give the title compound (202 mg, 65 %). ^{1}H NMR (400 MHz, DMSO) δ 13.87 (1H, br. s), 8.91 (1H, s), 7.55 (2H, d, *J* 9.0), 7.32 (2H, d, *J* 9.0).

Description 13 Methyl 4-amino-1,3-thiazole-5-carboxylate

A suspension of methyl 4-amino-2-methylthio-1,3-thiazole-5-carboxylate (6.74 g, 33 mmol) and Raney-Nickel (commercially available slurry in water, ca. 15 ml, added in 5 portions throughout the reaction) in ethanol (200 ml) was hydrogenated at 45 psi for 1 week. The catalyst was removed by filtration, washed with ethyl acetate and ethanol and the filtrate evaporated. The resulting solid was purified by flash column chromatography [eluant: ethyl acetate/ isohexane (1:4)] to give the title compound as a bright yellow solid (1.23 g, 24 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (1H, s), 5.90 (2H, brs), 3.84 (3H, s). *M/z* (ES$^+$) 159 (M+H$^+$).

Description 14 Methyl 4-(4-chlorophenylaminocarbonothioylamino)-1,3-thiazole-5-carboxylate

Description 13 (1.23 g, 7.8 mmol), 4-chlorophenyl isothiocyanate (1.33 g, 7.8 mmol) and a catalytic amount of 4-dimethylaminopyridine in acetonitrile was refluxed at 100 °C for 18 h. The reaction was cooled and the solid collected by filtration, washed with acetonitrile and methanol to give the title compound (0.79 g, 31 %). ^{1}H NMR (400 MHz, DMSO) δ 11.97 (1H, s). 10.13 (1H, s), 9.41 (1H, s), 7.71 (2H, d, *J* 8.8), 7.48 (2H, d, *J* 8.8), 3.89 (3H, s).

Description 15 6-(4-Chlorophenyl)-5-thioxo-5,6-dihydro[1,3]thiazolo[4,5-d] pyrimidin-7(4H)-one

Description 14 (788 mg, 2.4 mmol) was suspended in methanol (5 ml). Methanolic 1 M potassium hydroxide (10 ml, 9.6 mmol) was then added and the reaction stirred at room temperature for 2 h. The insoluble material was filtered, and the filtrate cooled to 0 °C and acidified to pH 5 with 1 N aqueous hydrochloric acid and the resulting solid filtered and washed with water. The solid was dry loaded onto silica in acetonitrile/ methanol and purified by flash column chromatography (eluant: 2.5 % methanol in dichloromethane) to give the title compound as a pink solid (200 mg, 28 %). ^{1}H NMR (400 MHz, DMSO) δ 14.37 (1H, s), 9.56 (1H, s), 7.54 (2H, d, *J* 8.7), 7.31 (2H, d, *J* 8.6). *M/z* (ES$^+$) 296, 298 (M+H$^+$).

Description 16 1-(4-Chlorophenyl)-9-methyl-2-thioxo-1,2,3,9-tetrahydro-6H-purin-6-one

Ethyl 5-amino-1-methyl-1*H*-imidazole-4-carboxylate (*Zhurnal Obshchei Khimii* 1987, 57 (3), 692) (0.50 g, 2.96 mmol) and 4-chlorophenyl isothiocyanate (0.50 g, 2.96 mmol) were stirred in pyridine (2.5 ml) at 45 °C for 17 h. The reaction was cooled and diluted by the addition of ice. When the ice had melted the reaction was filtered, the product rinsed with water and dried to give ethyl 5-(4-chlorophenylaminocarbonothioylamino)-1-methyl-1*H*-imidazole-4-carboxylate (0.75 g, 75 %). The solid was slurried in 1 % aqueous sodium hydroxide solution (7.5 ml) and heated at 80 °C for 90 min. The reaction was cooled, diluted with methanol to dissolve all solids and loaded onto a strong cation exchange (SCX)

cartridge. The cartridge was washed with methanol and then the product eluted with 2 M methanolic ammonia. The product was azeotroped with ethanol, triturated with acetonitrile and dried to give the title compound as an off white solid (0.63 g, 97 %).

^{1}H NMR (360 MHz, DMSO) δ 7.58 (1H, s), 7.37 (2H, m), 7.06 (1H, brs), 6.96 (2H, m), 3.54 (3H, s). *M/z* (ES$^+$) 293, 295 (M+H$^+$).

Description 17 Methyl-5-nitro-4-imidazolecarboxylate

Ammonium nitrate (3.2 g, 40.2 mmol) was added slowly to a solution of 4-imidazolecarboxylic acid (3.0 g, 26.8 mmol) in concentrated sulfuric acid (24 ml) at 100 °C. The reaction was heated for 2 days then cooled. Methanol (15 ml) was added cautiously with vigorous stirring and then the reaction heated at 60 °C for 24 h. The reaction was cooled and poured onto ice, causing a fine white precipitate to form. The mixture was neutralized by the addition of 33 % aqueous ammonia. The solid was filtered off and dried to give the title compound (1.24 g, 27 %). A second crop of crystals was collected from the filtrate (0.82 g, 18 %). ^{1}H NMR (400 MHz, DMSO) δ 14.2 (1H, brs), 7.94 (1H, s), 3.87 (3H, s).

Description 18 Methyl-5-amino-4-imidazolecarboxylate

A solution of Description 17 (1.24 g, 7.25 mmol) in 1:1 ethanol:methanol (60 ml) was hydrogenated using 10 % palladium on carbon catalyst under a balloon of hydrogen. After 4 h the reaction mixture was filtered, the filtrate condensed and azeotroped with ethanol. The product was triturated with ethyl acetate and dried to give the title compound as a white solid (0.98 g, 96 %). ^{1}H NMR (400 MHz, DMSO) δ 12.0 (1H, brs), 7.32 (1H, s), 5.56 (2H, s), 3.70 (3H, s). *M/z* (ES$^+$) 142 (M+H$^+$).

Description 19 1-(4-Chlorophenyl)-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one

Description 18 (0.98 g, 6.95 mmol) and 4-chlorophenyl isothiocyanate (1.29 g, 7.65 mmol) were stirred in pyridine (5 ml) at 100 °C. After 15 h additional 4-chlorophenyl isothiocyanate (0.12 g, 0.70 mmol) was added and heating continued for a further 4 h. The reaction was cooled, poured onto ice and the resultant solid, methyl 5-({[(4-chlorophenyl)amino]carbonothioyl}amino)-1*H*-imidazole-4-carboxylate, was collected by filtration and dried (0.42 g, 20 %). Without

purification, the solid was slurried in 1 % aqueous sodium hydroxide solution (10 ml) and heated at 80 °C for 2 h. The reaction was cooled and filtered to remove unreacted starting material. The filtrate was acidified to pH 5 using acetic acid, causing a fine white precipitate to form. The solid was collected, rinsed with water and dried to give the title compound as a fine white solid (0.28 g, 73 %). ^{1}H NMR (360 MHz, DMSO) δ 13.72 (2H, brs), 8.18 (1H, s), 7.55 (2H, m), 7.30 (2H, m). *M/z* (ES$^+$) 279, 281 (M+H$^+$).

Description 20 2-Thioxo-3-[4-trifluoromethylphenyl]-2,3-dihydropyrido[3,2-d] pyrimidin-4(1H)-one

Description 4 (0.20 g, 1.31 mmol) and 4-trifluoromethylphenyl isothiocyanate (0.32 g, 1.57 mmol) were heated at 75 °C in acetonitrile (5 ml) with a catalytic amount of 4-dimethylaminopyridine. After 16 h additional 4-(trifluoromethyl)phenyl isothiocyanate (50 mg, 0.25 mmol) was added and the reaction heated at 85 °C for a further 2 h . The reaction was cooled and the product collected by filtration, washed with acetonitrile (5 ml) and dried to give the title compound as a white solid (0.27 g, 90 %). ^{1}H NMR (360 MHz, DMSO) δ 13.14 (1H, s), 8.61 (1H, m), 7.90-7.76 (4H, m), 7.57 (2H, d, *J* 8.2). *M/z* (ES$^+$) 324 (M+H$^+$).

Description 21 3-Pyridin-3-yl-2-thioxo-2,3-dihydropyrido[3,2-*d*]pyrimidin-4(1*H*)-one

3-Aminopyridine-2-carboxylic acid (*Bioorg. Med. Chem.* 2001, 9, 2061) (1.84 g, 13.3 mmol) was treated with 3-pyridyl isothiocyanate according to the method of Description 7 to give the title compound directly, as an off white solid (1.33 g, 38 %). ^{1}H NMR (360 MHz, DMSO) δ 13.20 (1H, brs), 8.61 (2H, m), 7.80 (3H, m), 7.55 (1H, d, *J* 1.9), 7.56 (1H, m). *M/z* (ES$^+$) 257 (M+H$^+$).

Description 22 2-Chloro-*N*-(5-methylisoxazol-3-yl)acetamide

A solution of 3-amino-5-methylisoxazole (867 mg, 8.85 mmol) and triethylamine (2.4 ml, 17.7 mmol) in dichloromethane (10 ml) was added dropwise over 5 min to a solution of chloroacetyl chloride (0.707 ml, 8.85 mmol) in dichloromethane (15 ml) at 0 °C. The solution was allowed to warm to room temperature and stir for a further 2 h. The solution was then washed with 1:1 brine:water (2 x 20 ml) and

the dichloromethane layer dried over $MgSO_4$, filtered and evaporated. The resulting residue was triturated with diethyl ether to give the title compound (275 mg, 18 %). ^1H (360 MHz, DMSO) δ 11.25 (1 H, s), 6.62 (1 H, s), 4.29 (2 H, s), 2.38 (3 H, s). *M/z* (ES^+) 175, 177 ($M+H^+$).

Example 1 3-(4-Chlorophenyl)-2-[3-fluorobenzylthio]pyrido[3,4-d]pyrimidin-4(3H)-one

A suspension of Description 3 (0.50 g, 1.73 mmol), potassium carbonate (1.20 g, 8.70 mmol) and 3-fluorobenzyl bromide (0.34 g, 1.82 mmol) in acetonitrile (12 ml) was stirred at room temperature for 1 h. Additional 3-fluorobenzyl bromide (34 mg, 0.18 mmol) was added and the reaction stirred for a further hour. The reaction was diluted with water (50 ml), extracted with dichloromethane (2 x 50 ml) and the combined organic fractions dried over $MgSO_4$ and condensed. The crude product was purified by flash column chromatography, eluting with 2 % methanol in dichloromethane, to give the title compound as a white solid (100 mg, 15 %). ^1H NMR (400 MHz, $CDCl_3$) δ 9.10 (1H, s), 8.65 (1H, d, *J* 5.2), 7.99 (1H, dd, *J* 5.3, 0.8), 7.52 (2H, m), 7.23 (3H, m), 7.16 (1H, d, *J* 7.8), 7.10 (1H, m), 6.95 (1H, m), 4.42 (2H, s). *M/z* (ES^+) 398, 400 ($M+H^+$).

Example 2 3-(4-Chlorophenyl)-2-{2-(4-chlorophenyl)-2-oxoethylthio}pyrido[3,2-d]pyrimidin-4(3H)-one

A suspension of Description 5 (75 mg, 0.26 mmol), potassium carbonate (75 mg, 0.54 mmol) and 2-bromo-4'-chloroacetophenone (67 mg, 0.29 mmol) in acetonitrile (4 ml) was stirred at 75 °C for 5 h. The reaction was cooled and diluted with water (ca. 7 ml) to dissolve the salts. The solid was collected by filtration, rinsed with water (3 ml) then diethyl ether (5 ml) and dried to give the title compound as an off white solid (48 mg, 44 %). ^1H NMR (500 MHz, DMSO) δ 8.69 (1H, m), 8.10 (2H, m), 7.75-7.66 (5H, m), 7.57 (2H, m), 7.54 (1H, m), 4.77 (2H, s). *M/z* (ES^+) 442, 444 ($M+H^+$).

Examples 3-33

Examples 3-33 were prepared using the appropriate purinone or pyrimidinone core (Descriptions 5, 7, 8, 12, 15, 16, 19, 20 and 21) and the appropriate alkyl

iodide, bromide or chloride in a procedure analogous to Example 2. Alkyl iodides, bromides and chlorides are commercially available or described in Description 22 or prepared by known methods as follows: 1-(2-bromoethyl)-4-trifluoromethyl benzene, *Can. J. Chem.* 1996, 74, 453; 3-bromomethylbenzo[*b*]thiophene, *J. Med. Chem.* 2002, 45, 4559; 4-(2-bromoethyl)chlorobenzene, *J. Am. Chem. Soc.* 1977, 99, 3059. Where the product did not precipitate analytically pure from the reaction it was purified by recrystallisation, flash column chromatography, preparative thin layer chromatography or mass directed HPLC as appropriate.

EX	NAME	M/z ES+ [M+H+]	^{1}H NMR
3	3-(4-chlorophenyl)-2-[3-fluorobenzylthio]pyrido[3,2-d]pyrimidin-4(3H)-one	398, 400	(400 MHz, DMSO) δ 8.75 (1H, dd, *J* 4.3, 1.5), 8.12 (1H, dd, *J* 8.2, 1.5), 7.85 (1H, dd, *J* 8.2, 4.3), 7.64 (2H, d, *J* 8), 7.55 (2H, d, *J* 8), 7.35-7.25 (3H, m), 7.10-7.00 (1H, m), 4.45 (2H, s).
4	3-(4-chlorophenyl)-2-{2-(4-chlorophenyl)ethyl thio}pyrido[3,2-d] pyrimidin-4(3H)-one	428, 430	(400 MHz, DMSO) δ 2.94-2.96 (2 H, m), 3.34-3.37 (2 H, m), 7.31-7.37 (4 H, m), 7.53 (2 H, d, J8.6), 7.65 (2 H, d, J8.6), 7.85 (1 H, dd, J4.3, 8.2), 8.08 (1 H, dd, J1.6, 8.2), 8.75 (1 H, dd, J1.6, 4.3).
5	2-{5-chloro-1-benzothien-3-ylmethylthio}-3-(4-chlorophenyl)pyrido[3,2-d]pyrimidin-4(3H)-one	470, 472	(400 MHz, DMSO) d 4.71 (2 H, s), 7.42 (1 H, dd, *J*1.6, 8.6), 7.52 (2 H, d, *J*11.5), 7.63 (2 H, d *J*11.5), 7.88 (1 H, dd, *J* 4.3, 8.2), 8.01 (2 H, m), 8.08 (1 H, d, *J*2.0), 8.23 (1 H, dd, *J*1.6, 8.2), 8.76 (1 H, dd, *J*1.6, 4.3).
6	2-[1-benzothien-3-ylmethylthio]-3-(4-chlorophenyl)pyrido[3,2-d]pyrimidin-4(3H)-one	436, 438	(360 MHz, $CDCl_3$) d 8.82 (1H, dd, J 4.2, 1.8), 8.08 (1H, dd, J 8.4, 1.2), 7.85 (1H, m), 7.79 (1H, m), 7.69 (1H, dd, J 8.4, 4.1), 7.47 (3H, m), 7.38 (2H, m), 7.24 (2H, m), 4.71 (2H, s).

EX	NAME	M/z ES+ [M+H+]	^{1}H NMR
7	2-[1,3-benzothiazol-2-ylmethylthio]-3-(4-chlorophenyl)pyrido[3,2-d]pyrimidin-4(3H)-one	437, 439	(400 MHz, DMSO) δ 4.91 (2 H, s), 7.39-7.43 (1 H, m), 7.47-7.51 (1 H, m), 7.59 (2 H, d, J11.4), 7.68 (2 H, d, J11.5), 7.87 (1 H, dd, J 4.3, 8.2), 7.95 (1 H, dd, J 8.2, 1.2), 8.03 (1 H, dd, J1.7, 8.4), 8.11 (1 H, dd, J1.6, 8.2), 8.78 (1 H, dd, J1.6, 4.3).
8	3-(4-chlorophenyl)-2-[2-oxo-2-phenylethyl thio]pyrido[3,2-d] pyrimidin-4(3H)-one	408, 410	(400 MHz, DMSO) δ 4.79 (2 H, s), 7.54 (1 H, dd, J1.6, 8.2), 7.58-7.62 (4 H, m), 7.69-7.73 (4 H, m), 8.07-8.09 (2 H, d, m), 8.70 (1 H, dd, J1.6, 4.3).
9	3-(4-chlorophenyl)-2-{2-(3-chlorophenyl)-2-oxoethylthio}pyrido[3,2-d]pyrimidin-4(3H)-one	442, 444	(400 MHz, $CDCl_3$) δ 4.54 (2 H, s), 7.35 (2 H, d, J11.4), 7.50 (1 H, t, J7.8), 7.55-7.59 (4 H, m), 7.62-7.64 (1 H, m), 7.93-7.95 (1 H, m), 8.05-8.06 (1 H, m), 8.75-8.77 (1 H, m).
10	3-(4-chlorophenyl)-2-(2-oxo-2-[4-trifluoromethoxy phenyl]ethylthio)pyrido [3,2-d]pyrimidin-4(3H)-one	492, 494	(400 MHz, $CDCl_3$) δ 4.56 (2 H, s), 7.33-7.39 (4 H, m), 7.51-7.58 (4 H, m), 8.13 (2 H, d, J8.9), 8.76 (1 H, dd, J1.9, 4.3).
11	3-(4-chlorophenyl)-2-(2-oxo-2-[4-trifluoromethyl phenyl]ethylthio)pyrido [3,2-d]pyrimidin-4(3H)-one	476, 478	(400 MHz, $CDCl_3$) δ 4.58 (2 H, s), 7.36 (2 H, d, J11.6), 7.48-7.50 (1 H, m), 7.54-7.59 (3 H, m), 7.82 (2 H, d, J8.2), 8.18 (2 H, d, J8.2), 8.77 (1 H, dd, J1.6, 4.3).
12	3-(4-chlorophenyl)-2-{2-oxo-2-(4-pyrrolidin-1-yl phenyl)ethylthio}pyrido [3,2-d]pyrimidin-4(3H)-one	477, 479	(400 MHz, DMSO) δ 1.97-2.00 (4 H, m), 3.33-3.41 (4 H, m), 4.70 (2 H, s), 6.61 (2 H, d, J9.0), 7.58 (2 H, d, J9.0), 7.71 (2 H, d, J8.6), 7.77 (2 H, d, J3.1), 7.89 (2 H, d, J9.0), 8.70-8.72 (1 H, m).

EX	NAME	M/z ES+ [M+H+]	^{1}H NMR
13	3-(4-chlorophenyl)-2-[2-oxo-2-pyridin-2-ylethyl thio]pyrido[3,2-d] pyrimidin-4(3H)-one	409, 411	1H (400 MHz, $CDCl_3$) δ 4.87 (2 H, s), 7.35-7.40 (3 H, m), 7.51 (1 H, dd, J4.3, 8.2), 7.54-7.59 (3 H, m), 7.91 (1 H, td, J7.8, 1.6), 8.07 (1 H, dd, J1.2, 7.8), 8.74 (1 H, dd, J1.6, 4.3), 8.76-8.77 (1 H, m).
14	3-(4-chlorophenyl)-2-[4-fluorobenzylthio]pyrido [3,2-d]pyrimidin-4(3H)-one	398, 400	(400 MHz, DMSO) δ 4.42 (2 H, s), 7.09-7.11 (2 H, m), 7.48-7.55 (4 H, m), 7.64 (2 H, d, J8.6), 7.85 (1 H, dd, J4.3, 8.6), 8.13 (1 H, dd, J1.6, 8.2), 8.75 (1 H, dd, J1.6, 4.3).
15	2-[3-chlorobenzylthio]-3-(4-chlorophenyl)pyrido [3,2-d]pyrimidin-4(3H)-one	414, 416	(400 MHz, DMSO) d 4.43 (2 H, s), 7.28-7.34 (2 H, m), 7.42-7.44 (1 H, m), 7.54-7.56 (3 H, m), 7.64 (2 H, d, J8.6), 7.86 (1 H, dd, J4.3, 8.2), 8.13 (1 H, dd, J1.6, 8.2), 8.75 (1 H, dd, J1.4, 4.5).
16	3-(4-chlorophenyl)-2-[pyridin-2-ylmethylthio] pyrido[3,2-d]pyrimidin-4(3H)-one	381, 383	(400 MHz, DMSO) d 4.55 (2 H, s), 7.24-7.28 (1 H, m), 7.54-7.59 (3 H, m), 7.66 (2 H, d, *J*9.0), 7.72-7.76 (1 H, m), 7.84 (1 H, dd, *J*4.3, 8.2), 8.09 (1 H, dd, *J*1.6, 8.2), 8.47-8.49 (1 H, m), 8.75 (1 H, dd, *J*1.6, 4.3).
17	3-(4-chlorophenyl)-2-{5-phenyl-1,2,4-oxadiazol-3-ylmethylthio}pyrido[3,2-d]pyrimidin-4(3H)-one	448, 450	(400 MHz, DMSO) d 4.67 (2 H, s), 7.58-7.73 (7 H, m), 7.84 (1 H, dd, *J*4.3, 8.6), 8.04 (1 H, dd, *J*1.6, 8.6), 8.07-8.09 (2 H, m), 8.76 (1 H, dd, *J*1.6, 4.3).
18	2-{3-(4-chlorophenyl)-4-oxo-3,4-dihydropyrido[3,2-d]pyrimidin-2-ylthio}-N-(5-methylisoxazol-3-yl)acetamide	428, 430	(400 MHz, DMSO) d 2.35 (3 H, s), 4.11 (2 H, s), 6.56 (1 H, s), 7.59 (2 H, d, *J*8.6), 7.69 (2 H, d, *J*8.6), 7.81 (1 H, dd, *J*4.3, 8.2), 7.87 (1 H, dd, *J*1.6, 8.2), 8.73 (1 H, dd, *J*1.8, 4.1), 11.27 (1 H, s).

EX	NAME	M/z ES+ [M+H+]	^{1}H NMR
19	3-(4-chlorophenyl)-2-[3-fluorobenzylthio]thieno [2,3-d]pyrimidin-4(3H)-one	403, 405	(400 MHz, $CDCl_3$) δ 7.49 (2H, m), 7.43 (1H, d, J 6.0), 7.23 (3H, m), 7.14 (1H, d, J 6.0), 7.10 (1H, m), 7.07 (1H, m), 6.94 (1H, m), 4.35 (2H, s).
20	3-(4-chlorophenyl)-2-[3-fluorobenzylthio]thieno [3,2-d]pyrimidin-4(3H)-one	403, 405	(500 MHz, DMSO) d 8.24 (1H, d, *J*5.3), 7.63 (2H, d, *J*8.7), 7.52 (2H, d, *J*8.7), 7.45 (1H, d, *J*5.3), 7.36-7.31 (1H, m), 7.30-7.24 (2H, m), 7.10-7.03 (1H, m), 4.40 (2H, s).
21	3-(4-chlorophenyl)-2-{2-(4-chlorophenyl)-2-oxoethylthio}thieno [3,2-d]pyrimidin-4(3H)-one	447, 448	(500 MHz, $CDCl_3$) d 8.01 (2H, d, J 8.3), 7.72 (1H, d, J 5.3), 7.54 (2H, d, J 8.5), 7.50 (2H, d, J 8.4), 7.32 (2H, d, J 8.4), 6.94 (1H, d, J 5.2), 4.52 (2H, s).
22	6-(4-chlorophenyl)-5-[3-fluorobenzylthio][1,3] thiazolo[5,4-d]pyrimidin-7(6H)-one	404, 406	(400 MHz, DMSO) δ 9.11 (1H, s), 7.65 (2H, d, *J* 8.6), 7.53 (2H, d, *J*8.6), 7.38-7.30 (1H, m), 7.30-7.19 (2H, m), 7.11-7.03 (1H, m), 4.41 (2H, s).
23	6-(4-chlorophenyl)-5-{2-(4-chlorophenyl)-2-oxoethylthio}[1,3]thiazolo [5,4-d]pyrimidin-7(6H)-one	448, 450	(400 MHz, DMSO) δ 9.04 (1H, s), 8.05 (2H, d, *J*, 8.6), 7.71 (2H, d, *J*8.6), 7.65 (2H, d, *J*8.6), 7.58 (2H, d, *J*8.6), 4.77 (2H, s).
24	6-(4-chlorophenyl)-5-{2-(4-chlorophenyl)-2-oxoethylthio}[1,3]thiazolo [4,5-d]pyrimidin-7(6H)-one	448, 450	(400 MHz, DMSO) d 4.84 (2 H, s), 7.59 (2 H, d, J8.7), 7.65 (2 H, d, J8.6), 7.71 (2 H, d, J8.8), 8.07 (2 H, d, J8.6), 9.57 (1 H, s).
25	2-{5-chloro-1-benzothien-3-ylmethylthio}-1-(4-chlorophenyl)-9-methyl-1,9-dihydro-6H-purin-6-one	473, 475	(500 MHz, $CDCl_3$) d 7.80 (1H, d, J 2.0), 7.26 (1H, d, J 8.6), 7.68 (1H, s), 7.47 (3H, m), 7.34 (1H, dd, J 8.6, 2.0), 7.20 (2H, d, J 8.6), 4.60 (2H, s), 3.82 (3H, s).

EX	NAME	M/z ES+ [M+H+]	^{1}H NMR
26	1-(4-chlorophenyl)-9-methyl-2-(2-[4-trifluoromethylphenyl] ethylthio)-1,9-dihydro-6H-purin-6-one	465, 467	(400 MHz, $CDCl_3$) d 7.68 (1H, s), 7.57 (2H, d, J 8.1), 7.50 (2H, d, J 8.5), 7.33 (2H, d, J 7.8), 7.20 (2H, d, J 8.5), 3.81 (3H, s), 3.66 (2H, t, J 7.8), 3.07 (2H, t, J 7.8).
27	1-(4-chlorophenyl)-2-{2-(4-chlorophenyl)ethyl thio}-9-methyl-1,9-dihydro-6H-purin-6-one	431, 433	(400 MHz, DMSO) δ 2.96 (2 H, t, J7.6), 3.33 (2 H, t, J7.6), 3.78 (3 H, s), 7.28 (2 H, d, J8.2), 7.35 (2 H, d, J8.2), 7.42 (2 H, d, J9.0), 7.63 (2 H, d, J8.6), 8.03 (1 H, s).
28	1-(4-chlorophenyl)-2-{2-(4-chlorophenyl)-2-oxoethylthio}-9-methyl-1,9-dihydro-6H-purin-6-one	445, 447	(500 MHz, $CDCl_3$) d 8.00 (2H, d, J 8.7), 7.57 (1H, s), 7.52 (4H, m), 7.29 (2H, d, 8.7), 4.48 (2H, s), 3.37 (3H, s).
29	1-(4-chlorophenyl)-2-[3-fluorobenzylthio]-9-methyl-1,9-dihydro-6H-purin-6-one	401, 403	(400 MHz, $CDCl_3$) δ 7.66 (1H, s), 7.49 (2H, d, J 8.6), 7.26 (1H, m) 7.21 (2H, d, 8.6), 7.12 (2H, m), 6.96 (1H, m), 4.33 (2H, s), 3.82 (3H, s).
30	1-(4-chlorophenyl)-2-[3-fluorobenzylthio]-1,9-dihydro-6H-purin-6-one	387, 389	(400 MHz, DMSO) δ 13.55 and 13.35 (1H, brs), 8.23 and 8.03 (1H, brs), 7.62 (2H, m), 7.48 (2H, m), 7.33 (1H, m), 7.30 (2H, m), 7.07 (1H, m), 4.39 (2H, s).
31	2-{2-(4-chlorophenyl)-2-oxoethylthio}-3-[4-trifluoromethylphenyl] pyrido[3,2-d]pyrimidin-4(3H)-one	476, 478	(400 MHz, $CDCl_3$) δ 8.78 (1H, dd, *J* 3.9, 2.0), 8.01 (2H, d, *J* 8.6), 7.87 (2H, dd, *J* 8.2), 7.60-7.52 (6H, m), 4.57 (2H, s).
32	2-[3-fluorobenzylthio]-3-[4-trifluoromethyl phenyl]pyrido[3,2-d] pyrimidin-4(3H)-one	432	(400 MHz, $CDCl_3$) δ 8.83 (1H, dd, *J* 4.5, 1.4), 8.02 (1H, dd, *J* 8.2, 1.6), 7.81 (2H, dd, *J* 8.2), 7.71 (1H, dd, *J* 8.4, 4.5), 7.47 (2H, d, *J* 8.2), 7.27 (1H, m), 7.15-7.09 (2H, m), 6.98-6.93 (1H, m), 4.41 (2H, s).

EX	NAME	M/z ES+ [M+H+]	1H NMR
33	2-(methylthio)-3-pyridin-3-ylpyrido[3,2-d]pyrimidin-4(3H)-one	271	(360 MHz, DMSO) d 3.40 (3H, s), 7.65 (1 H, m), 7.84 (1 H, m), 8.02 (2 H, m), 8.70 (1 H, d, J 1.8), 8.75 (2H, m).

Example 34 3-(4-Chlorophenyl)-2-(3-oxo-4-phenylpiperazin-1-yl)pyrido [3,2-d]pyrimidin-4(3H)-one

A mixture of Description 6 (50 mg, 0.17 mmol), 1-phenylpiperazin-2-one (*Tetrahedron Lett.* 1998, 39, 7459) (37 mg, 0.21 mmol) and potassium carbonate (240 mg, 1.7 mmol) in anhydrous acetonitrile (2 ml) was refluxed for 5 h. The reaction was cooled to room temperature and the salts removed by filtration and washed with acetonitrile (3 x 10 ml). The filtrate was evaporated *in vacuo* and the resulting residue purified by mass directed HPLC, then passed through a strong cation exchange (SCX) cartridge to give the title compound (8 mg, 10 %). ^{1}H (400 MHz, DMSO) δ 8.65 (1H, dd, *J* 1.6, 4.3), 7.94 (1H, dd, *J* 1.6, 8.2), 7.77 (1H, dd, *J* 4.1, 8.4), 7.64-7.61 (4H, m), 7.40-7.36 (2H, m), 7.26-7.22 (3H, m), 3.86 (2H, s), 3.43 (4H, s). *M/z* (ES$^+$) 432, 434 (M+H$^+$).

Example 35 3-4-Chlorophenyl-2-{2-(4-chlorophenyl)ethylamino}pyrido [3,2-d]pyrimidin-4(3H)-one

A mixture of Description 6 (58 mg, 0.2 mmol) and 2-(4-chlorophenyl)ethylamine (37 mg, 0.24 mmol) and potassium carbonate (138 mg, 1 mmol) in acetonitrile (2 ml) was heated at reflux for 4 h, then cooled to room temperature. The reaction mixture was then evaporated *in vacuo* and the residue partitioned between dichloromethane (15 ml) and water (2 x 15 ml). The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude product was purified by preparative thin layer chromatography (eluant: 5% methanol in dichloromethane) to give the title compound as a beige solid (20 mg, 24 %). ^{1}H (360 MHz, DMSO) δ 8.43 (1 H, dd, *J* 1.4, 4.2), 7.75-7.72 (1 H, m), 7.64-7.59 (3 H, m), 7.37 (2H, d, *J* 8.6), 7.33 (2H, d, *J* 8.5), 7.21 (2H, d, *J* 8.4), 6.07 (1H, t, *J* 5.8), 3.50-3.45 (2H, m), 2.82 (2 H, t, *J* 7.0). M/z (ES$^+$) 411, 413 (M+H$^+$).

Example 36 3-(4-Chlorophenyl)-2-[3-fluorobenzyloxy]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

To 3-fluorobenzylalcohol (16 mg, 0.127 mmol) in THF (1 ml) at 0 °C was added NaH (60 % dispersion in oil, 5 mg, 0.130 mmol) and the solution allowed to warm to room temperature for 10 min. A solution of Description 10 (25 mg, 0.084 mmol) in THF (1 ml) was added and the reaction stirred for 18 h at room temperature. The reaction was concentrated, then dissolved in water (2 ml) and dichloromethane (2 ml) and the mixture vortexed. After settling, the mixture was added to a phase separation cartridge and the dichloromethane phase was separated and concentrated. The crude mixture was dissolved in dimethylsulfoxide and purified by mass-directed HPLC to give the title compound as a white solid (10 mg, 30 %). ^{1}H (400 MHz, DMSO) δ 8.20 (1H, d, *J* 4.7), 7.59 (2H, d, *J* 7.7), 7.51 (2H, d, *J* 7.7), 7.35 (2H, m), 7.08 (2H, m), 6.99 (1H, d, *J* 8.8), 5.42 (2H, s). M/z (ES$^+$) 387, 389 (M+H$^+$).

Example 37 3-(4-Chlorophenyl)-2-[3-fluorobenzylamino]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

Description 10 (25 mg, 0.084 mmol), 3-fluorobenzylamine (12 mg, 0.105 mmol) and potassium carbonate (35 mg, 0.254 mmol) in acetonitrile (1.5 ml) were heated to reflux for 4 h. The solvent was removed and the reaction then dissolved in water (2 ml) and dichloromethane (2 ml) added and the mixture vortexed. After settling, the mixture was added to a phase separation cartridge and the dichloromethane phase was separated and concentrated. The crude mixture was dissolved in dimethylsulfoxide and purified by mass-directed HPLC to provide the title compound as a white solid (9 mg, 27 %). ^{1}H (400 MHz, DMSO) δ 7.74 (1H, d, *J* 5.3), 7.57 (2H, d, *J* 8.3), 7.29 (3H, m), 7.14 (1H, d, *J* 5.3), 6.95 (3H, m), 4.62 (2H, d, *J* 5.4), 4.47 (1H, brm). M/z (ES$^+$) 386, 388 (M+H$^+$).

The above exemplified compounds of the present invention have been tested in the following assay and generally possess an IC_{50} < 300nM and, in the majority of cases, < 200 nM. Other assays, such as electrophysiology using rat VR1 expressed in HEK cells measuring activity at various pH levels, can be used.

Biological Methodology

Determination of *in vitro* activity

CHO cells, stably expressing recombinant human VR1 receptors and plated into black-sided 384-well plates, were washed twice with assay buffer (Hepes-buffered saline) and then incubated with 1uM Fluo-3-AM for 60 minutes in darkness. Cells were washed twice more to remove excess dye, before being placed, along with plates containing capsaicin and test compounds in a Molecular Devices FLIPR. The FLIPR simultaneously performed automated pharmacological additions and recorded fluorescence emmission from Fluo-3. In all experiments, basal fluorescence was recorded, before addition of test compounds and subsequent addition of a previously determined concentration of capsaicin that evoked 80% of the maximum respsonse. Inhibition of capsaicin evoked increases in intracellular $[Ca^{2+}]$ were expressed relative to wells on the same plate to which capcaicin was added in the absence of test compounds. Increases in intracellular $[Ca^{2+}]$ occuring after addition of test compound alone, prior to addition of capsaicin, allow determination of intrinsic agonist or partial agonist activity, if present.